M.4 HUMAN HEALTH STUDIES: EPIDEMIOLOGY

Various epidemiologic studies have been conducted at some of the sites evaluated in this PEIS because of the concern for potential health effects (that is, premature fatalities) associated with the manufacture and testing of nuclear weapons. These studies focus on the DOE workforce and residents of communities, surrounding DOE sites.

M.4.1 BACKGROUND

The health effects associated with ionizing radiation exposure were first published about 60 years ago. Studies published in the 1930s first documented cancer among painters who used radium to paint watch dials back in 1910-1920. Radiation therapy for disease was used since the 1930s, and studies have shown that the risk of cancer was related to the amounts of radiation received. Nuclear weapons research and manufacture and consequent exposure to radiation occurred beginning in the late 1930's. Exposure to radionuclides has changed over time with higher levels occurring in the early days of research and production. Numerous epidemiologic studies have been conducted among workers who manufactured and tested nuclear weapons due to the concern with potential adverse health effects. More recently, concerns about radiologic contaminants off-site have resulted in health studies among communities that surround DOE facilities. The following section briefly gives an overview of epidemiology followed by a review of epidemiologic studies of sites evaluated in the PEIS.

Epidemiology is the study of the distribution and determinants of disease in human populations. The distribution of disease is considered in relation to time, place, and person. Relevant population characteristics should include the age, race and sex distribution of a population, as well as other characteristics related to health, such as social characteristics (for example, income and education), occupation, susceptibility to disease, and exposure to specific agents. Determinants of disease include the causes of disease, as well as factors that influence the risk of disease.

M.4.1.1 Study Designs

Ecologic Studies. Ecologic studies compare the frequency of a disease in groups of people in conjunction with simple descriptive studies of geographical information in, an attempt to determine how health events among populations vary with levels of exposure. These groups may be identified as the residents of a neighborhood, a city, or a county where demographic information and disease or mortality data are available. Exposure to specific agents may be defined in terms of residential location or proximity to a particular area, such as distance from a waste disposal site. An example of an ecologic study is a comparison of the rate of heart disease among community residents by drinking water quality.

The major disadvantage of ecologic studies is that the measure of exposure is based on the average level of exposure in the community, when we are really interested in the individual's exposure. Ecologic studies do not take into account other factors, such as age and race that may also be related to disease. These types of studies may lead to incorrect conclusions, an "ecologic fallacy." For the above example, it would be incorrect to assume that the level of water hardness influences the risk of getting heart disease. Despite the obvious problems with ecologic studies, they can be a useful first step in identifying possible associations between risk of disease and environmental exposures. However, because of their potential for bias they should never be considered more than an initial step in investigation of disease causation.

Cohort Studies. The cohort study design is a type of epidemiologic study frequently used to examine occupational exposures within a defined workforce. A cohort study requires a defined population that can be classified as being exposed or not exposed to an agent of interest, such as radiation or chemicals that influence the probability of occurrence of a given disease. Characterization of the exposure may be qualitative (for example, high, low, or no exposure) or very quantitative (for example, radiation measured in Sieverts [Sv] and

chemicals in parts per million). Surrogates for exposure, such as job titles, are frequently used in the absence of quantitative exposure data.

Individuals enumerated in the study population are followed for a period of time to observe who died. In general overall rates of death and cause-specific rates of death have been assessed for workers at the PEIS sites. Death rates for the exposed worker population are compared with death rates of workers who did not have the exposure (internal comparison), or compared with expected death rates based on the U.S. population or State death rates (external comparison). If the rates of death differ from what is expected, an association is said to exist between the disease and exposure. In cohorts where the exposure has not been characterized, excess mortality can be identified, but these deaths cannot be attributed to a specific exposure, and additional studies may be warranted. More recent studies have looked at other disease endpoints, such as overall and cause-specific cancer incidence (newly diagnosed) rates.

Most cohort studies at PEIS sites have been historical cohort studies, that is, the exposure occurred some time in the distant past. These studies rely on past records to document exposure. This type of study can be problematic if exposure records are incomplete or were destroyed. Cohort studies require extremely large populations that have been followed for many (20-30) years. They are generally difficult to conduct and are very expensive. These studies are not well suited to studying diseases that are rare. Cohort studies do, however, provide a direct estimate of the risk of death from a specific disease, and allow an investigator to look at many disease endpoints.

Case-Control Studies. The case-control study design starts with the identification of persons with the disease of interest (case) and a suitable comparison (control population of persons without the disease). Controls must be persons who are at risk for the disease and are representative of the population that generated the cases. The selection of an appropriate control group is often quite problematic. Cases and controls are then compared with respect to the proportion of individuals exposed to the agent of interest. Case-control studies require fewer persons than cohort studies, and therefore, are usually less costly and less time consuming, but are limited to the study of one disease (or cause of death). These types of studies are well suited for the study of rare diseases and are generally used to examine the relationship between a specific disease and exposure.

M.4.1.2 Definitions

Unfamiliar terms frequently used in epidemiologic studies, including those used in this document, are defined below.

Age, gender, and cigarette smoking are the principal determinants of mortality. Standardization is a statistical method used to control for the effects of age, gender, or other characteristics so that death may be compare among different population groups. There are two ways to standardize rates, the indirect or direct methods. In general the indirect method of standardization is most frequently used.

Indirect standardization: The disease rates in the reference (comparison) population are multiplied by the number of individuals in the same age and gender group in the study population to obtain the expected rate of disease for the study population.

Direct standardization: The disease rates in the study population are multiplied by the number of individuals in the same age and gender group in the reference (comparison) population. This gives the expected rates of disease for the reference population if these rates had prevailed in that group.

Standardized mortality ratio (SMR): The SMR is the ratio of the number of deaths observed in the study population to the number of expected deaths. The expected number of deaths is based on a reference (or comparison population). Death rates for the U.S. population (or State) are most frequently used as the comparison to obtain expected rates. An SMR of 1 indicates a similar risk of disease in the study population

compared with the reference population. An SMR greater than 1 indicates excess risk of disease in the study population compared with the reference group, and an SMR less than 1 indicates a deficit of disease.

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Relative risk: The ratio of the risk of disease among the exposed population to the risk of disease in the unexposed population. Relative risks are estimated from cohort studies.

Odds ratio: The ratio of the odds of disease if exposed, to the odds of disease if not exposed. Under certain conditions, the odds ratio approaches the relative risk. Odds ratios are estimated from case-control studies.

Excess Relative Risk (ERR): Per SV is based on a regression model in which the relative risk is assumed to be of the form $1 + \beta Z$, where Z is the cumulative dose in SV.

Standardized Rate Ratio (SRR): A rate ratio in which the numerator and the denominator have been standardized to the same (standard) population distribution.

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Healthy Worker Effect: A phenomenon observed in studies of occupational diseases. Workers usually exhibit lower overall death or disease rates compared to the general population, due to the fact that the severely ill and disabled are excluded from employment. Rates from the general population may be inappropriate for comparison if this effect is not taken into consideration.

Confidence Interval (CI): A range of values for a variable of interest, for example, a rate, constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits.

P, P (Probability) Value: The probability that a test statistic would be as extreme as or more extreme than observed if the null hypothesis were true. The letter P, followed by the abbreviation n.s. (not significant) or by the symbol < (less than) and a decimal notation such as 0.01, 0.05, is a statement of the probability that the difference observed could have occurred by chance, if the groups are really alike, that is, under the *Null Hypothesis*. Investigators may arbitrarily set their own significance levels, but in most biomedical and epidemiologic work, a study result whose probability value is less than 5 percent ($P < 0.05$) or 1 percent ($P < 0.01$) is considered sufficiently unlikely to have occurred by chance to justify the designation "statistically significant."

Multivariate Analysis: A set of techniques used when the variation in several variables has to be studied simultaneously. In statistics, any analytic method that allows the simultaneous study of two or more *Dependent Variables*.

Incidence: (*Syn:incident number*) The number of instances of illness commencing, or of persons falling ill, during a given period in a specified population. More generally, the number of new cases of a disease in a defined population, within a specified period of time. The term incidence is sometimes used to denote *Incidence Rate*.

Incidence Rate: The rate at which new events occur in a population. The numerator is the number of new events that occur in a defined period; the denominator if the population at risk of experiencing the event during this period, sometimes expressed as person-time. The incidence rate most often used in public health practice is calculated by the formula

$$\frac{\text{Number of new events in specified period}}{\text{Number of persons exposed to risk during this period}} \times 10^n$$

In a dynamic population, the denominator is the average size of the population, often the estimated population at the mid-period. If the period is a year, this is the annual incidence rate. This rate is an estimate of the person-time incidence rate, that is, the rate per 10^n person-years. If the rate is low, as with many chronic diseases, it is also a good estimate of the cumulative incidence rate. In follow-up studies with no censoring, the incidence rate is calculated by dividing the number of new cases in a specified period by the initial size of the cohort of persons being followed; this is equivalent to the cumulative incidence rate during the period. If the number of new cases during a specified period is divided by the sum of the person-time units at risk for all persons during the period, the result is the person-time incidence rate.

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M.4.2 HANFORD SITE

Surrounding Community

Sever et al. published two studies in 1988 of birth defects in Benton and Franklin Counties in which Hanford is located (AJE 1988a:226-242, 243-254). The prevalence of births of congenital malformed infants for the study period from 1968 to 1980 was the focus of one of the two studies (AJE 1988a:243-254). The congenital malformation rate in the newborn population of 19.6/1000 was not elevated compared with the rates for the States of Washington, Idaho, and Oregon (12.2 / 1000). Neural tube defects were more common than expected in the comparison area (Prevalence=1.72; 95% CI=1.22-2.34). The companion case-control study investigated whether there was any association of parental occupational exposure to external radiation and the risk of congenital malformations among births occurring from 1957 to 1980 (AJE 1988a:226-242). Two defects, congenital dislocation of the hip (12 observed, 7.1 expected, $p<0.025$) and tracheoesophageal fistula (4 observed, 1.4 expected, $p<0.05$), showed statistically significant association with parental employment at Hanford but not with parental radiation exposure.

Neural tube defects showed a significant association with parental preconception external radiation exposure. Other defects studied, including Down's Syndrome, showed no evidence of such an association with parental external radiation exposure.

Jablon et al. examined cancer mortality in populations living near nuclear facilities in the U.S., including Hanford (JAMA 1991a:1403-1408). The study compared cancer mortality in 107 counties with or near 62 nuclear facilities to those in comparison counties with similar demographic characteristics but without nuclear facilities. For Hanford, Benton, Franklin, and Grant Counties were studied. The authors concluded that no general association was detected between residents in a county with a nuclear facility and death attributable to leukemia or any other form of cancer. The authors also noted that interpretation of the study results is limited by the study's ecological approach in which the exposures of individuals are not known.

Worker Studies

Mancuso and Sanders Era

Studies of the Hanford workers began in 1969. Initially, the study of Hanford workers conducted by the University of Pittsburgh was designed to evaluate longevity and disability in workers (HP 1978a:521-538). Hanford workers were compared with their brothers or sisters and to a national sample of employed people from the Social Security Administration continuous work history files. The study included 17,600 males and 3,900

females hired from 1944 through 1971, and considered deaths that occurred from 1944 to October 1972. Workers were categorized as "radiation exposed workers" and "nonexposed workers." In general, the longevity for both males and females within each category were similar, with the largest difference for exposed men who had a nonsignificantly reduced longevity relative to their sibling controls. A second analysis included about 1,800 Hanford workers; 1,800 matched Social Security Administration continuous work history controls; and 3,055 "identified siblings." The disability claim rate for all Hanford workers was significantly lower than the matched Social Security Administration continuous work history controls, as was the rate for radiation-exposed workers.

Analyses were expanded to examine specific causes of death (HP 1977a:369-385). In these analyses, the average cumulative radiation dose for workers dying of a site specific cancer, or group of cancers, was compared with the average radiation dose for all workers dying from all causes.

For deaths from 1944-1972, the following cancer types were reported with higher radiation doses: multiple myeloma, pancreas, brain, kidney, lung, colon, myeloid leukemia, and lymphomas. When the comparison was made against the average dose for all noncancer deaths rather than for all deaths, excess deaths were attributed to radiation for all cancers combined, multiple myeloma, myeloid leukemia, pancreas, and lung.

The authors examined the amount of radiation necessary to double the risk of death for specific cancers. Five cancer categories were concluded to have significant doubling doses: bone marrow cancers, pancreatic cancer, lung cancer, reticuloendothelial neoplasms, and all cancers combined. Next, the authors explored whether the doses received at some specific ages were more important than at other ages, and they concluded that sensitivity to radiation carcinogenesis was high before age 25 years and after age 45 years.

As the analytic methods used in the study were controversial, the Hanford data were re-analyzed by other investigators in 1979, and the analytic methods were reassessed. Hutchinson et al. concluded that analyses of the Hanford data, adjusted for age and calendar year of death, reduced the number of cancer sites for which a radiation dose relationship could be suggested to two: cancer of the pancreas ($p=0.011$ for trend test) and multiple myeloma ($p=0.009$ for trend test) (HP 1979a:207-220). For both of these sites, more deaths were observed than expected only among those with doses exceeding 10 rad. The authors also considered the issue of sensitive ages for radiation exposure and concluded such ages could not be identified without considering lifetime patterns of exposure ages.

In a separate independent analysis, Gofman et al. considered these issues using a different methodological approach (HP 1979a:617-639). The authors reported, consistent with the finding of Hutchinson et al., that differences in radiation dose between those dying of cancer compared with other diseases are found primarily in those receiving 10 rad or more exposure. The authors estimated that radiation caused a 3.5 percent increment in cancer deaths. The doubling dose for cancers overall was estimated at 43.5 rad, consistent with the Mancuso estimate previously reported. The authors did not concur with Mancuso et al. on the suggestion of variation in sensitivity to radiation by age at exposure.

Other methodological problems in the original analyses were identified by Anderson who concluded that the estimate of excess deaths was "implausible," but did agree that the analyses were consistent with some excess deaths from multiple myeloma, cancer of the pancreas, and possibly lung cancer (HP 1978b:743-750). A deficit in leukemia deaths was noted. The Mancuso study was also reviewed by the National Radiological Protection Board (NRPB) in the United Kingdom. This report concluded that the only excess fatal malignancies at Hanford that may be associated with radiation are cancer of the pancreas and multiple myeloma (NRPB 1978a). The report indicated that further investigation was necessary, as the effect could have been due to other carcinogens.

In 1978, Kneale, Stewart, and Mancuso updated the Hanford study with death information to 1977 (IAEA 1978a:387-412). The authors concluded that approximately 5 percent of the cancer deaths at Hanford were

radiation- induced and that these extra deaths were probably concentrated among cancers of the bone marrow, lung, and pancreas.

In 1981, Kneale et al. again reported on the Hanford data, using a different analytic technique (BJIM 1981a:156-166). The cohort included radiation-monitored employees up to 1975 and deaths through 1977. The authors estimated a linear model doubling dose at 15 rads, estimated the latency to be 25 years, and rejected the hypothesis that all age at exposure groups are equally sensitive to radiation.

In 1993, Kneale and Stewart published a re-analysis of the Hanford data (AJIM 1993a:371-389). The study included 27,395 male and 8,473 female workers who worked between 1944 and 1978 and had been monitored for radiation. Deaths were determined through 1986. In this analysis, all cancers listed on the death certificate were included in the study. The authors concluded that the Hanford data supported a doubling dose from 8.6 to 44.8 mSv, with a nonlinear dose response, in contrast to the prior study. The estimated proportion of radiation-caused cancers ranged from 12.5 percent to 50.9 percent, the cancer latency period was estimated to be 14-17 years, and the most radiosensitive ages for exposure were over 58 years of age.

In 1996, Stewart and Kneale again investigated the relationship between age at exposure and cancer risk in the Hanford data using monitored workers described in the 1993 analysis (OEM 1996a:225-230). The data were adjusted to account for the effects of date of birth and date of death. The workers were grouped by average doses into intervals of when dose was received to allow for cancer latency and age groups to isolate the most sensitive age at exposure.

The authors concluded that sensitivity to carcinogenic effects of radiation increase progressively with age during adult life and providing that the dose is too small to produce many cell deaths, the ratio of leukemias to solid tumors is no different for radiogenic and idiopathic tumors in contrast with the atomic bomb survivor data, which found a strong association with leukemia.

Simultaneously, other researchers were reporting the results of studies of the Hanford workers. In 1979, Gilbert and Marks reported the results of analyses of the mortality experience of Hanford workers from the time the plant was built through April 1974 (RR 1979a:122-148). The cohort consisted of 20,842 white males hired before 1966 with a focus on 13,075 employed at least 2 years. Mortality rates were not higher than expected among workers for all causes of death, all malignant neoplasms, diseases of the circulatory system, accidents, or other causes. When individual cancer sites were considered, only malignant neoplasm of the pancreas (SMR=130, $p<0.05$) among individuals who had worked less than 2 years at Hanford was significantly elevated.

To determine if there was an association with external radiation exposure, the mortality experience of workers who had been monitored for radiation was compared with all workers in the study. Among white males monitored for radiation, there was a statistically significant trend between mortality and increasing radiation dose for pancreatic cancer (4 observed, 2.5 expected; $p=0.07$ for trend test) and multiple myeloma (12.4 observed, 3.6 expected; $p=0.006$ for trend test) when lagged 2 years for cancer development. When exposures were lagged for 10 years, only deaths due to multiple myeloma (6.2 observed, 1.5 expected; $p=0.006$ for trend test) showed a trend with cumulative occupational exposure to ionizing radiation.

The mortality experience of the Hanford cohort was updated the following year (RR 1980a:740-741). Three hundred and ninety additional deaths among white males, occurring to May 1977, were included in the study. Results were similar to those previously reported.

The cohort was again updated in 1983 (RR 1983a:211-213). This analysis was expanded to include workers hired during and after 1965 and employed 2 or more years. In this analysis, the significant positive trend between increasing dose and pancreatic cancer disappeared. The significant trend for multiple myeloma remained.

The next update of the cohort mortality study for Hanford was published in 1989 (HP 1989a:11-25). The cohort consisted of 31,500 males and 12,600 females first employed through 1978. Deaths from 1944-1981 were analyzed for the entire cohort. Death certificates for radiation-monitored workers who died in the State of Washington between 1982-1985 were also obtained.

Overall, Hanford workers continued to have death rates substantially below the general U.S. population. Among female workers not monitored for external radiation, there were significantly more deaths for the category of accidents, poisonings, and violence than expected (SMR=1.38, p=0.05). Monitored females had a higher rate of death from diseases of the musculoskeletal system and connective tissues than expected (SMR=2.33, p=0.05). When individual cancer sites were considered, males not monitored for radiation were observed to have significantly higher rates of death from pancreatic cancer (SMR=1.69, p=0.01) and solid tumors (SMR=1.56, p=0.05) than expected.

The risk analyses for trends by radiation dose were lagged for 2- and 10-year induction periods, and included deaths from 1947 through 1981. No correlation between mortality and dose was seen when the analyses were lagged for 2 years. When dose was lagged 10 years, there was a suggestive trend between dose and deaths from all cancers, genital cancer among females, and multiple myeloma.

Although the number of workers at Hanford with Pu deposition was limited, data on these workers were analyzed separately to examine major cause of death categories by exposure categories. No trends between increasing death rates and increasing deposition Pu were detected. As cause of death information was available through 1985 for those dying in the State of Washington, additional analyses were conducted. Four additional deaths from multiple myeloma were observed, but the trend with dose was not statistically significant.

The Hanford cohort was once again updated by Gilbert et al. in 1993 (HP 1993a:577-590). This analysis included workers who were employed 6 months or more and were first employed through 1978. Deaths among the entire cohort that occurred from 1944 through 1986, and through 1989 for monitored workers who died in the State of Washington, were analyzed. This data set included 456 workers not previously studied and eliminated 265 individuals who never actually worked at the site. Radiation dose records from construction worker files were also added to the data set.

When the death rates for Hanford workers were compared with the general U.S. population, monitored females continued to have an elevated rate of deaths from musculoskeletal system and connective tissue conditions (SMR=2.06, p=0.05) noted in the 1989 paper. As previously reported, unmonitored males continued to have higher death rates for pancreatic cancer (SMR=1.57, p=0.05) and the category noted as miscellaneous solid tumors (SMR=1.47, p=0.05).

As in previous papers, the data were then analyzed to examine trends between the risk of death and external radiation dose lagged for 2 and 10 years. Statistically significant trends were seen when the dose was lagged 10 years for deaths due to pancreatic cancer (SMR=1.59, p=0.065), Hodgkin's disease (SMR=1.80, p=0.038), and multiple myeloma (SMR=1.54, p=0.10). Deaths due to liver cancer (SMR=1.93, p=0.065) were detected when the exposures were lagged for 2 years. Additional analyses were conducted, which included "all" cancers noted on the death certificate, in addition to those reported on the death certificate as the "underlying cause of death." The investigators concluded that there were no additional cancers that showed significant correlations with dose as compared with the previous analysis that used the underlying cause of death.

Hanford workers have been included in several studies that have examined occupational risks across the nuclear complex, both in the U.S. and internationally. These combined studies have been undertaken in an attempt to increase the statistical power of the studies to detect the effects of low-level chronic radiation exposure.

A combined site mortality study included workers from Hanford, Oak Ridge, and Rocky Flats (RR 1993a:408-421). Earlier analyses of these cohorts indicated that risk estimates calculated through

extrapolation from high-dose data to low-dose data did not seriously underestimate risks of exposure to low-dose radiation (AJE 1990a:917-927; RR 1989a:19-35). The updated analyses were performed in order to determine whether the extrapolated risks represented an over-estimation of the true risk at low doses. The study population consisted of white males employed at one of the three facilities for at least 6 months and monitored for external radiation. The Hanford population also included females and nonwhite workers. The total population dose was 1237 Sv. Analyses included trend tests for site-specific cancer deaths and several broad noncancer categories. Statistically significant trends were noted for cancer of the esophagus (p=0.015 for trend test), cancer of the larynx (p=0.019 for trend test), and Hodgkin's disease (p=0.048 for trend test). These cancers were not related to radiation exposure levels in previously published studies. Excess relative risk models were calculated for the combined DOE populations and for each DOE site separately. Without exception, all risk estimates included the possibility of zero risk (that is, the confidence interval for the risk coefficient went from below zero to above zero). There was evidence of an increase in the excess relative risk for cancer with increasing age in the Hanford and Oak Ridge populations; both populations showed significant correlations of all cancer with radiation dose among those 75 years and older.

Multiple myeloma (p=0.103 for trend test) was the only cancer found to exhibit a statistically significant correlation with radiation exposure that was based on the excess previously reported among Hanford workers.

An international effort to pool data from populations exposed to external radiation included Hanford workers, as well as workers at Rocky Flats and Oak Ridge in the U.S. and other radiation worker populations in Canada and Britain (RR 1995a:117-132). The cohort compared 95,673 workers employed 6 months or longer and the population dose was 3,543.2 Sv. There was no evidence of an association between radiation dose and mortality from all causes or from all cancers. There was a significant dose-response relationship with leukemia, excluding chronic lymphocytic leukemia (ERR=2.18 per Sv; 90 percent CI 0.1-5.7) and multiple myeloma (ERR not computed; 44 observed; p=0.037 for trend test). The study results do not suggest that current radiation risk estimates for cancer at low levels of exposure are appreciable in error.

Epidemiologic Studies

DOE's Office of Epidemiologic Studies has implemented an epidemiologic surveillance program at Hanford to monitor the health of current workers. This program will evaluate the occurrence of illness and injury in the workforce on a continuing basis and the results will be issued in annual reports. The implementation of this program will facilitate an ongoing assessment of the health and safety of Hanford's workforce and will help identify emerging health issues.

Currently operational at a number of DOE sites, including production sites and research and development (R&D) facilities, epidemiologic surveillance uses routinely collected health data including descriptions of illness resulting in absences lasting 5 or more consecutive workdays, disabilities, and OSHA recordable injuries and illnesses abstracted from the OSHA 200 log. These health event data, coupled with demographic data about the active workforce at participating sites, are analyzed to evaluate whether particular occupational groups are at increased risk of disease or injury when compared with other workers at a site. As the program continues and data for an extended period of time become available, time trend analysis will become an increasingly important part of the evaluation of worker health. Monitoring the health of the workforce provides a baseline determination of the illness and injury experience of workers and a tool for monitoring the effects of changes made to improve the safety and health of workers. Noteworthy changes in the health of the workforce may indicate the need for more detailed study or increased health and safety measures to ensure adequate protection for workers.

Memorandum of Understanding

The Hanford Environmental Dose Reconstruction (Hanford Environmental Dose Reconstruction) Project was undertaken by DOE to estimate the radiation dose that people may have received from nuclear operations at

Hanford (WA Ecology 1994a). In 1990, DOE entered into a Memorandum of Understanding with the Department of Health and Human Services to conduct health studies at DOE sites. The Centers for Disease Control and Prevention's National Center for Environmental Health is responsible for dose reconstruction studies and has managed the Hanford Environmental Dose Reconstruction Project since that time.

The study determined that the largest doses to offsite populations were from iodine-131 released into the air in large quantities between December 1944 and December 1947. The most important radiation exposure pathway for iodine-131 was the consumption of milk produced by cows grazing on pasture downwind of Hanford. The doses to the thyroid gland of individuals near Hanford were larger than those farther from the site, and depended on the iodine-131 deposition and quantity of milk consumed at each location.

A second pathway of potential importance was the Columbia River. Releases to the river from Hanford were highest in the years 1956-1965, which was the height of reactor operations at Hanford. The most important means of exposure from the river pathway was the consumption of fish by local residents. However, maximum doses for the heaviest consumption of fish were estimated to be about half the dose an individual normally receives each year from all sources of radioactive materials in the U.S. environment. This study is in its final stages and will be completed shortly.

A study in the United Kingdom linked a father's exposure to ionizing radiation in the workplace with the subsequent risk of leukemia in his children (RR=6.42; 95 percent CI=1.57-26.3) (BMJ 1990a:423-434). A study was undertaken to replicate this study in other similar populations. Hanford was one of three sites selected for study by NIOSH. The population under study consists of residents of Benton and Franklin Counties. The study includes leukemia, non-Hodgkin's lymphoma, and central nervous system tumors diagnosed from 1957-1991 in children under the age of 15. The study is expected to be completed in 1996.

A number of studies of the Hanford workforce are underway, directed by NIOSH, under the Memorandum of Understanding.

Researchers at the University of Texas Medical Branch are conducting a cohort mortality study of female nuclear weapons workers exposed to low levels of ionizing radiation and other workplace physical and chemical agents at 12 DOE facilities, including Hanford. The study will be completed in 1997.

A study of multiple myeloma among workers exposed to ionizing radiation and other physical and chemical agents is being conducted by the University of North Carolina at various DOE sites, including Hanford. The study is expected to be completed in 1996-1997.

An epidemiologic evaluation of childhood leukemia and paternal exposure to ionizing radiation is being conducted by Battelle Columbus. The study will collect information of selected childhood cancers, residential history, and the father's exposure to ionizing radiation. Completion of the study is expected in 1996-1997.

An epidemiologic study of leukemia at four DOE sites is being conducted by NIOSH. Sites selected for the study include Hanford.

Boston University is conducting a health-effects-of-job-stress study associated with the redesign and reconfiguration of the nuclear weapons industry. This study will identify how specific practices for managing change affect individual health and work performance and to recommend ways to minimize health effects in the future. Hanford is one of seven DOE facilities included in this multisite study. The study will begin in 1996 and is scheduled for completion in 1999.

A comprehensive occupational health surveillance project at Hanford will design and implement a health surveillance system at the site. The University of Washington and the Hanford Environmental Health Foundation will conduct the study. Completion is expected in 1998.

A study of heat stress among carpenters at Hanford will assess the real effects of heat stress on physiologic functions in a real work situation. The study is being conducted by Michigan State University and the United Brotherhood of Carpenters' Health and Safety Fund. The study is scheduled for completion in 1999.

Other Related Studies

The Hanford Thyroid Disease Study began in 1988 under the management of Centers for Disease Control and will be completed in 1998 (HF FHCRC 1995a). It was initiated based on preliminary information from the Hanford Environmental Dose Reconstruction Project indicating that releases of radioactive iodine-131 from Hanford in its early years may have produced exposures to human thyroids large enough to have affected the gland's functioning. About 3,200 people living at various distances from Hanford have been located and are now being examined for thyroid disease and thyroid function. These people were selected because as infants during the years of peak releases of iodine-131 they were the most sensitive population group. Information gathered from the individuals in the study about their diet, milk consumption, age, sex, and place of residence will be used to calculate individual doses received by the thyroid gland using the models developed in the Hanford Environmental Dose Reconstruction Project. The study results are expected in 1998.

M.4.3 NEVADA TEST SITE

Surrounding Communities. Above ground testing of nuclear weapons at the NTS Test Range Complex in southern Nevada between 1951 and 1958 resulted in the dissemination of radioactive fallout over southeastern Nevada and southwestern Utah through wind dispersion. Several epidemiologic studies have been conducted to investigate possible health effects of low-level radiative fallout on residents of these States. These studies focused on leukemia and thyroid disease in children downwind of NTS.

A series of ecologic studies showed equivocal results in potentially exposed children. A cross sectional review of thyroid modularity among teenage children reported by Weiss et al. found no significant difference in the frequency of nodules among "potentially exposed" and "not exposed" children (AJPH 1971a:241-249). Exposure was defined in terms county of residence. Rallison et al. reported no significant difference in any type of thyroid disease between Utah children exposed to fallout radiation in the 1950s and control groups drawn from Utah and Arizona (AJM 1974a:457-463; JAMA 1975a:1069-1072).

To investigate the possible relationship between childhood leukemia and radioactive fallout, Lyon et al. conducted a mortality study of Utah-children under 15 years old who died in Utah between 1944 and 1975 (NEJM 1979a:397-402). Lyon et al. selected this age group because of the reported increased susceptibility of children to the neoplastic effects of radiation and the lack of a comparison group over 14 years of age with suitable low exposures. Lyon et al. obtained death certificates from the Utah vital statistics registrar and based on year of death, categorized decedents into either high (fallout years of 1951-1958) or low exposure periods (combined pre-fallout years of 1944-1950 and post-fallout years of 1959-1975). From estimated fallout patterns contained in maps of 26 tests, Lyon et al. categorized 17 southern rural counties high fallout area and the remaining northern urban counties as low fallout areas. Age-specific mortality rates derived for deaths which occurred in the combined low exposure periods were compared with those in the high exposure period. For reasons unknown, leukemia mortality during the low exposure periods in high fallout counties was half that of the United States and Utah. A significant excess of leukemia occurred among children statewide who died during the high fallout period compared to those who died during the low fallout periods (SMR=1.40, 95 percent CI=1.08-1.82, $p<0.01$). This excess was more pronounced among those who resided in the high fallout area (SMR=2.44, 95 percent CI=1.18-5.03). No pattern was found for other childhood cancers in relation to fallout exposure. A radiation dosage was not available, and the effect of migration were not determined for this study.

Beck and Krey reconstructed exposure of Utah residents studied by Lyon et al. (Science 1983a:18-24) to external gamma-radiation from NTS fallout through measurements of residual cesium-137 and Pu in soil

(NEJM 1979a:397-402). Beck and Krey found that residents in southwest Utah closest to NTS received the highest exposures, but noted that residents of urban northern areas received a higher mean dose and a significantly greater population dose than did residents of most counties closer to the test site. Northern Utah residents received higher average bone doses than southern Utah residents; therefore, the distance from NTS should not be the sole criteria for dividing the State into geographic subgroups for the purpose of conducting epidemiologic studies. Beck and Krey concluded that bone doses to southern Utah residents were too low to account for the excess leukemia deaths identified by Lyon et al. They also determined that bone and whole body doses from NTS fallout were small relative to lifetime doses most Utah residents receive from background radiation, and that it was unlikely that these exposures would have resulted in any observed health effects.

Land et al. attempted to confirm the association between leukemia and fallout reported by Lyon et al. using cancer mortality data from the National Center for Health Statistics for the period 1950 through 1978 (NEJM 1979a:397-402); (Science 1984a:139-144). No statistically significant differences in mortality from leukemia or other childhood malignancies between northern (SRR=1.52, 90 percent CI=1.24-1.87) and southern Utah (SRR=1.49, 90 percent CI=0.88-2.51) were observed. The observed difference in leukemia mortality between the border and interior counties was opposite in direction to that reported by Lyon et al. Results indicated a downward trend in childhood leukemia mortality over time. Eastern Oregon and the State of Iowa also were selected for comparison with Utah. The leukemia mortality rate for eastern Oregon was higher (SRR=1.81, 90 percent CI=1.07-3.07), and Iowa lower (SRR=1.16, 90 percent CI=1.02-1.31) than the rate for Utah (SRR=1.49, 90 percent CI=0.88-2.51. Land et al. concluded that these results suggest that the association reported by Lyon et al. merely reflects an unexplained low leukemia rate in southern Utah for the period 1944 to 1949.

Another study that assessed the development of cancer among individuals potentially exposed to radioactive fallout has been reported by Rallison et al. (HP 1990c:739-746). This study examined the thyroid neoplasia risk in a cohort of children born between 1947 and 1954 in two counties near nuclear test sites, one in Utah and one in Nevada. A comparison group of Arizona children presumed to have no fallout exposure was also evaluated. The children (11 to 18 years of age) were examined between 1965 and 1968 for thyroid abnormalities and were reexamined in 1985 and 1986. Children living in the nuclear testing (Utah/Nevada) area had a higher rate of thyroid neoplasia (5.6/1000 for phase 1 and 24.6/1000 for phase 2) than the comparison children in Arizona (3.3/1000 for phase and 20.2/1000 for phase 2), but the differences were not statistically significant (RR=1.2, p=0.65 for phase 2). The authors concluded that living near the NTS in the 1950s has not resulted in a statistically significant increase in thyroid neoplasms.

A study by Johnson examined cancer incidence in a cohort of families that were members of the Church of Jesus Christ of Latter-Day Saints in southwest Utah near the NTS (JAMA 1984b:230-236). The study compared cancer incidence among all Utah members of the Church of Jesus Christ of Latter-Day Saints during the period 1967-1975 with cancer incidence among two exposed populations: persons residing in a "high fallout area"' and an "exposure effects group" residing in a broader area that received less intense exposure from radioactive fallout. Limitations of the study include: the inability to locate 40 percent of the defined population; the lack of verifying the reported diagnosis of cancer; and the inability to interview a comparable control group.

Cancer incidence for both exposed groups was compared with that of all Utah members of the Church of Jesus Christ of Latter-Day Saints for two time periods, 1958-1966 and 1972-1980. Johnson found an apparent increased incidence of leukemia (19 cases, 3.6 expected, p=0.01) and cancers of the thyroid (6 observed, 1.4 expected, p=0.01) and bone (3 observed, 0.3 expected, p=0.01) for residents of the high fallout area for both time periods. Additional analyses suggested that a higher proportion of the cancers among exposed groups were in radiosensitive tissues and the proportional excess increased with time compared with all Utah members of the Church of Jesus Christ of Latter-Day Saints. The ratio of radiosensitive cancers to all other cancers from 1959-1966 was 24 percent higher among the "high fallout area" group and 29.6 percent higher among those in the "fallout effects" group. For 1972-1980, the ratio was 53.3 percent higher in the "high fallout area" group and 300 percent higher in the "fallout effects" group.

Machado examined cancer mortality rates of a three-county region in southwestern Utah in comparison to the remainder of Utah (AJE 1987c:44-61). There was no excess risk of cancer mortality in southwest Utah, with the exception of leukemia (OR=1.45, 90 percent CI=1.18-1.79 with Utah controls), which showed a statistically significant excess for all ages combined, and for children age 0-14. In fact, mortality from all cancer sites combined was lower in southwest Utah than the remainder of the State. The authors noted that their findings, including those for leukemia, were inconsistent with the cancer incidence study conducted by Johnson (JAMA 1984b:230-236).

Archer measured soil, milk, and bone strontium-90 levels to identify states with high-, intermediate and low-fallout contamination (AEH 1987a:263-271). He then correlated the deaths from radiogenic and nonradioactive leukemias with the time periods of above ground nuclear testing both in the United States and Asia. The results show that leukemia deaths in children were higher in States with high exposure and lower in States with less exposure. He showed that leukemia deaths in children peaked approximately 5.5 years following nuclear testing peaks. The last leukemia peak in the United States occurred in 1968 to 1969, 5.5 years after the last year of a 3-year period of intensive testing in Asia. The increases were seen in the radiogenic leukemias (myeloid and acute leukemias), and not with "all other leukemias."

Kerber et al. updated a previously identified cohort of children living in portions of Utah, Nevada, and Arizona, to estimate individual radiation doses and determine thyroid disease status through 1985-1986 (JAMA 1993a:2076-2082). Of the 4,818 children originally examined between 1965-1970, 2,473 were included in the followup exam. Outcomes of interest included thyroid cancers, neoplasms, and nodules based on physical examinations of the thyroid. Exposure of the thyroid to radioiodines was based on radionuclide deposition rates provided by DOE and surveys of milk producers. Children with questionable findings were referred to a panel of endocrinologists for further examination. The authors reported an excess number of thyroid neoplasms (combined benign and malignant) and a positive dose-response trend for neoplasms, both of which were statistically significant. The authors also reported a positive dose-response trend for thyroid nodules, not statistically significant, and a positive dose-response trend for thyroid carcinomas with marginal statistical significance. The authors estimated that an excess of between 1 and 12 neoplasms (between 0 to 6 excess malignancies was probably caused by exposure to radioiodines from the nuclear weapons testing. A letter to the editor criticized Kerber et al. for relying on food histories obtained 22 years after the fact to depict radioiodine intake, and for the untested modeling approach-for determining dose to the thyroid (JAMA 1994a:825-826). These concerns were addressed by Kerber et al., which acknowledged the uncertainties in the dose estimates, but concluded that their estimates were conservative (JAMA 1994a:826).

Till et al. estimated doses to the thyroid of 3,545 subjects who were exposed to radioiodine fallout from NTS (HP 1995a:472-483). The U.S. Public Health Service first examined this cohort for thyroid disease between 1965-70 and later in 1985-86. Till et al. assigned individual doses based on age, residence histories, dietary histories, and lifestyle. Individualized dose and uncertainty was combined with the results of clinical examinations to determine the relationship between dose from NTS fallout and thyroid disease incidence.

Workers. Military personnel and civilian employees of the Department of Defense observed and participated in maneuvers at the NTS Test Range Complex during above ground tests. An excess number of leukemia cases was reported (9 cases, 3.5 expected) among the 3,224 men who participated in military maneuvers in August 1957 at the time of the nuclear test explosion "Smoky" (JAMA 1980a:1575-1578). The participants were located and queried on their health status, diseases, or hospitalizations as of December 1981. Various Federal records systems were linked, including clinical files, and next of kin was queried about cause of death for those participants who were deceased. Exposure information was available from film badged records, and the mean gamma dose for the entire cohort was 466.2 mrem. In a later report of the same cohort, the number of incident cases of leukemia had increased to 10 with 4 expected (O/E=2.5, 95 percent CI=1.2-4.6) (JAMA 1983a:620-624). No excess in "total cancers" was observed, however. In addition, four cases of polycythemia vera were reported where 0.2 was expected (JAMA 1984a:662-664). The excess in leukemia cancer incidence and mortality appear to be limited to the soldiers who participated in "Smoky."

The leukemia excess was not observed in a National Research Council mortality study of soldiers exposed to five series of tests at two sites: Nevada Test Site (PLUMBBOB) and the Pacific Proving Ground (DOE 1985b). The National Research Council reported that the number of leukemia cases in "Smoky" was greater, but the increase was considered nonsignificant when analyzed with the data from the other four tests. In 1989, however, it was discovered that the roster of the atomic veterans cohort on which the National Research Council based its 1985 study contained misclassification errors. As a result, this study is being reanalyzed, and the National Research Council anticipates publishing the new results by 1997.

M.4.4 IDAHO NATIONAL ENGINEERING LABORATORY

Surrounding Communities

Jablon et al. examined cancer mortality in populations living near nuclear facilities in the U.S., including INEL in Idaho (JAMA 1991a:1403-1408). The study compared cancer mortality from 1950-1984 in 107 counties with or near 62 nuclear facilities with cancer mortality in control counties without nuclear facilities. Cancer mortality for Bingham, Butte, and Jefferson Counties, where INEL is located, was compared with nine control counties in the same region, with similar demographic characteristics. The authors concluded that no general association was detected between residents in a county with a nuclear facility and death attributable to leukemia or any other form of cancer. The authors noted that interpretation of the study results is limited by the study's ecological approach in which the exposures of individuals are not known.

Cancer morbidity and mortality data in two additional counties near INEL, Clark and Minidoka, were reviewed by the Idaho Department of Health and Welfare (ID DHW 1991a; ID DHW 1991b). Clark County lies northeast of INEL and Minidoka County southwest of INEL. Cancer death rates were examined for the years 1950-1989 and cancer incidence rates for the years 1978-1987 to determine if any significant trends in cancer morbidity and mortality could be observed in these counties compared with the entire State. No statistically significant differences in age- and sex-adjusted death rates were observed in either county.

When cancer incidence data were considered, the overall cancer incidence rate in Clark County was higher than expected based on the State of Idaho's experience. When the Clark County data were examined by primary site, only two sites were found to be significantly higher than expected—female breast cancer (8 cases observed vs. 3.2 expected, p=0.05) and lip cancer (3 cases observed vs. 0.4 expected, p=0.05). In Minidoka County, there was no increase in overall cancer incidence rate compared with the entire State. Examination by primary sites in Minidoka County, however, showed three cancer sites were found to be increased—cancer of the stomach (20 cases observed vs. 11.6 expected, p=0.05), lip (23 cases observed vs. 8 expected, p=0.01), and uterus (40 cases observed vs. 24.2 expected, p=0.01). These studies also suffered from the limitations inherent in ecological studies. In addition, the authors noted that too many comparisons were made for "significant" results and that the data for Clark County, with an estimated population of 800, were too small to make meaningful analyses.

State Health Agreement Program

In 1991, INEL completed a historical dose reconstruction study to examine the impact of radioactive materials released to the environment during INEL's past operations. Subsequently, under the State Health Agreement program managed by the DOE Office of Epidemiologic Studies, a grant was awarded to the State of Idaho to convene an expert panel to review the final dose reconstruction report. The State panel evaluated the environmental transport and dose assessment models used for the dose reconstruction and recommended that additional work, involving public participation, be done to more fully examine offsite consequences (ID DHW 1993a).